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The Timing of Congenital Diaphragmatic Hernia Repair on Extracorporeal Membrane Oxygenation Impacts Surgical Bleeding Risk

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ABSTRACT

Background: The optimal timing of surgical repair for infants with congenital diaphragmatic hernia (CDH) treated with extracorporeal membrane oxygenation (ECMO) support remains controversial. The risk of surgical bleeding is considered by many centers as a primary factor in determining the preferred timing of CDH repair for infants requiring ECMO support. This study compares surgical bleeding following CDH repair on ECMO in early versus delayed fashion.
Methods: A retrospective review of 146 infants who underwent CDH repair while on ECMO support from 1995 to 2021. Early repair occurred during the first 48 h after ECMO cannulation (ER) and delayed repair after 48 h (DR). Surgical bleeding was defined by the requirement of reoperative intervention for hemostasis or decompression.
Results: 102 infants had ER and 44 infants DR. Surgical bleeding was more frequent in the DR group (36% vs 5%, $p < 0.001$) with an odds ratio of 11.7 (95% CI: 3.48–39.3, $p < 0.001$). Blood urea nitrogen level on the day of repair was significantly elevated among those who bled (median 63 mg/dL, IQR 20–85) vs. those who did not (median 9 mg/dL, IQR 7–13) ($p < 0.0001$). Duration of ECMO support was shorter in the ER group (median 13 vs 18 days, $p = 0.005$). Survival was not statistically different between the two groups (ER 60% vs. DR 57%, $p = 0.737$).
Conclusion: We demonstrate a significantly lower incidence of bleeding and shorter duration of ECMO with early CDH repair. Azotemia was a strong risk factor for surgical bleeding associated with delayed CDH repair on ECMO.
Level of evidence: Level III cohort study.

1. Introduction

The optimal timing of surgical repair for infants with congenital diaphragmatic hernia (CDH) treated with extracorporeal membrane oxygenation (ECMO) support remains controversial. Some centers prefer early repair on ECMO, yet there is no standardized definition of early repair. Other centers repair when infants are close to decannulation to have the "protection" of ECMO support during the repair, but when the likelihood of decannulation, and therefore the cessation of anticoagulation, is in close proximity. Lastly, CDH repair following successful decannulation from ECMO remains a strategy performed by many centers. Retrospective studies support all these strategies, with some suggesting that the timing of repair does not meaningfully impact the patient outcome [1–4]. There are no prospective randomized trials to address this question. Confounding variables such as severity of pulmonary hypoplasia, pulmonary hypertension, cardiorespiratory and ECMO management algorithm differences between centers, and other anomalies, including cardiac defects, would make a large matched cohort prospective randomized trial exceptionally difficult. Many centers consider the risk of surgical bleeding while on ECMO to be a

Abbreviations: CDH, congenital diaphragmatic hernia; ECMO, extracorporeal membrane oxygenation; PPLV, percent predicted lung volume; MRI, magnetic resonance imaging; BUN, blood urea nitrogen; Cr, creatinine level; PTT, partial thrombin time; ACT, activated clotting time; CDHSG, Congenital Diaphragmatic Hernia Study Group; IQR, interquartile range; OR, odds ratio; CI, confidence interval; CPR, Cardiopulmonary resuscitation.

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primary factor leading to the preference to avoid CDH repair while on ECMO support [5–9].

Proponents of early repair suggest that CDH repair will improve respiratory mechanics, promote lung expansion and growth, and possibly improve pulmonary hypertension leading to higher survival, with the most severe patients necessitating repair to achieve successful ECMO decannulation for any chance for survival [10–12]. Multiple centers report low surgical bleeding rates with an approach of early repair, with some using aminocaproic acid or tranexamic acid as adjunctive hemostatic agents [13–15]. Alternatively, studies promoting CDH repair following ECMO decannulation cite higher survival than surgical repair on ECMO and negligible risk for surgical bleeding [16,17]. However, there is a quantifiable mortality in the non-repair group that must be accounted for in overall survival using this strategy. In patients unable to wean and decannulate prior to repair, the decision to either redirect care based on “non-survivable” disease or attempt repair as a last-ditch effort must be made [18,19].

The primary aim of this study is to evaluate the impact of timing of CDH repair on surgical bleeding in a large single-center cohort of infants repaired at different time points while on ECMO support. Outcomes of survival and ECMO duration were also examined.

2. Methods

A retrospective review of medical records of all infants with CDH that had a repair on ECMO at Boston Children's Hospital, a large tertiary center with a dedicated CDH program, from May 1995 to December 2021 was conducted under an approved institutional review board protocol (IRB-P00022152). Infants who underwent surgical repair after ECMO decannulation and ECMO support following surgical repair were excluded from detailed analysis.

2.1. Data collection

Data collected included sex, gestational age at birth, birth weight, prenatal diagnosis, percent predicted lung volume (PPLV) on fetal magnetic resonance imaging (MRI), which was available after 2005 [20–22], laterality of the defect, liver position, and inborn status (Table 1). Additional post-natal characteristics included Congenital Diaphragmatic Hernia Study Group (CDHSG) defect size classification, liver position, presence of cardiac defects, use of chest compressions for resuscitation prior to the initiation of ECMO, operative timing of CDH repair after the initiation of ECMO. We definied postoperative surgical bleeding as the need for operative intervention for decompression and/or hemostasis. We additionally reviewed chart data and progress notes to identify patient factors that could be construed as deserving to be labelled as “unstable on ECMO”. We collected data regarding the details of interventions for postoperative hemorrhage, duration of ECMO, survival to discharge, stroke identified on imaging, blood urea nitrogen level (BUN) and the creatinine level (Cr) on the day of operative repair, and acute renal failure requiring dialysis. CDHSG defect size was documented for cases after 2007 and was determined based on author review of operative notes for cases prior to 2007 [23]. We further looked at the operating surgeons regarding case volume and bleeding complication rate.

2.2. Early vs. delayed repair

The two groups compared were early and late repair on ECMO. Early repair (ER) was defined as repair within the first 48 h of ECMO initiation and delayed repair (DR) after 48 h of ECMO initiation. The surgical approach for CDH repairs on ECMO support was open laparotomy, with Gortex patch placement when required based on defect size.

2.3. Anticoagulation

Anticoagulation during ECMO therapy was managed with heparin infusion. Heparin titration was based primarily on the activated clotting time (ACT, goal range 180–220s) from 1995 to 2010 and anti-Xa levels (goal range 0.3–0.7 IU/mL) from 2010 to 2016. From 2016 to 2018 heparin titration was based on ACT and partial thrombin time (PTT, goal range 60–85s) levels. PTT levels were used during the entire study period as adjunctive data during heparin administration. Anticoagulation was decreased or even suspended for periods in patients who had significant postoperative bleeding throughout the study. Additionally, perioperative aminocaproic acid infusion was used as an adjunct therapy to decrease the operative bleeding risk for all patients on ECMO support, using bolus dose of 100 mg/kg followed by continuous infusion of 30 mg/kg/hr [13,14]. Postoperative abdominal bleeding was identified by physical exam, dropping hemoglobin level, increased transfusion requirement, and imaging studies. Hemothorax was defined by high volume tube thoracostomy output greater than 100 mL per day accompanied by a fall in hemoglobin. Acute renal failure was defined by oliguria that required hemodialysis for fluid and/or electrolyte/acid-base management.

2.4. Statistical analyses

Continuous variables were reported as mean and standard deviation if normally distributed or as the median and interquartile range (IQR) if not normally distributed. Categorical variables were reported as frequencies and percentages. We conducted a univariate analysis to compare the two groups of early and delayed repairs concerning demographic and perinatal features, ECMO duration, and postoperative findings. Fisher's exact test was used to compare the timing of repair groups on categorical variables and Mann–Whitney tests to compare them on continuous variables. We applied multivariable logistic regression using backward

Table 1
Patient demographics.

Patient Demographics and Perinatal Features	Overall (n = 146)	ER (n = 102, 70%)	DR (n = 44, 30%)	P
Male, n (%)	81 (55%)	55 (54%)	26 (59%)	0.564
Prenatal diagnosis, n (%)	118 (81%)	85 (83%)	33 (75%)	0.241
PPLV, median (IQR)	15 (11–18)	15 (10–18)	15 (12–18)	0.615
Inborn, n (%)	100 (68%)	75 (74%)	25 (57%)	**0.046**
Gestational age (weeks), median (IQR)	38 (37–39)	38 (37–39)	39 (38–40)	0.066
Birth weight (grams), median (IQR)	3000 (2700–3400)	3000 (2600–3300)	3000 (2800–3450)	0.352
Cardiac defect, n (%)	19 (13%)	14 (14%)	5 (11%)	0.794
CDH left-sided, n (%)	101 (69%)	70 (69%)	31 (71%)	0.826
CDH liver-up, n (%)	128 (88%)	89 (87%)	39 (89%)	0.999
CDH high-risk defect (type C and D), n (%)	125 (86%)	88 (86%)	37 (84%)	0.949

PPLV: percent predicted lung volume; CDH: congenital diaphragmatic hernia. IQR: interquartile range. Bold = P value statistically significant.

Table 2
Postoperative results.

ECMO therapy and postoperative course	Overall (n = 146)	ER (n = 102, 70%)	DR (n = 44, 30%)	p
CPR before ECMO, n (%)	21 (14%)	11 (11%)	10 (23%)	0.073
Days on ECMO, median (IQR) [min, max]	14 (9–22) [1, 94]	13 (8–20) [1, 94]	18 (11–25) [6, 44]	**0.005**
Surgical site bleeding, n (%)	21 (14%)	5 (5%)	16 (36%)	**<0.001**
Stroke*, n (%)	37 (25%)	26 (25%)	11 (25%)	0.95
BUN, mg/dL (IQR)	9 (7–16)	8 (6–11)	33 (18–71)	**<0.001**
Cr, mg/dL (IQR)	0.6 (0.5–0.7)	0.6 (0.5–0.7)	0.6 (0.5–0.9)	0.528
BUN/Cr, median (IQR)	15 (11–33)	13 (10–16)	66 (30–83)	**<0.001**
BUN/Cr ratio > 20	50 (34%)	15 (15%)	35 (80%)	**<0.001**
ARF (required dialysis), n (%)	26 (18%)	14 (14%)	12 (27%)	0.05
Survival, n (%)	86 (59%)	61 (60%)	25 (57%)	0.737

ECMO: extracorporeal membrane oxygenation; CPR: cardiopulmonary resuscitation; BUN: blood urea nitrogen; Cr: creatinine; ARF: acute renal failure; IQR: interquartile range. (*Stroke here defined as abnormality on brain imaging). Bold = P value statistically significant.

stepwise selection and the likelihood ratio test to identify significant independent factors associated with surgical bleeding with risk estimated by the odds ratio (OR) and 95% confidence interval (CI). Statistical analysis was conducted using IBM SPSS Statistics version 27.0 (IBM Corporation, Armonk, NY). A two-tailed $p < 0.05$ was considered statistically significant [24].

3. Results

Between May 1995 and December 2021, 451 infants with CDH were treated at Boston Children's Hospital, of which 167 utilized ECMO support and underwent surgical repair. Only three infants (2%) had surgical repair following ECMO decannulation, and 18 infants had ECMO support following CDH repair (11%). Excluding these 21 infants, 146 remained for analysis that had CDH repair while on ECMO support. No patients in this study had CDH repair on ECMO as a "salvage plan", but rather all cases were treated with the planned intent for operative repair as a necessary step towards the goal of survival.

Of 146 infants evaluated, 102 (70%) were repaired during the first 48 h after ECMO cannulation (ER), and 44 (30%) had repair after 48 h (DR) while still on ECMO. There were no statistically significant differences between groups comparing sex, gestational age, birth weight, prenatal diagnosis, cardiac defects, PPLV, right vs. left-sided defect, and liver herniation, or CDHSG defect sizes (Table 1). The early repair group had significantly more inborn patients, and there was a trend towards significance in the DR group for CPR prior to ECMO cannulation ($p = 0.073$) (Table 2).

Surgical bleeding requiring reoperation was more frequent in the DR vs. ER group (36% vs. 5%, $p < 0.001$) with an odds ratio of 11.7

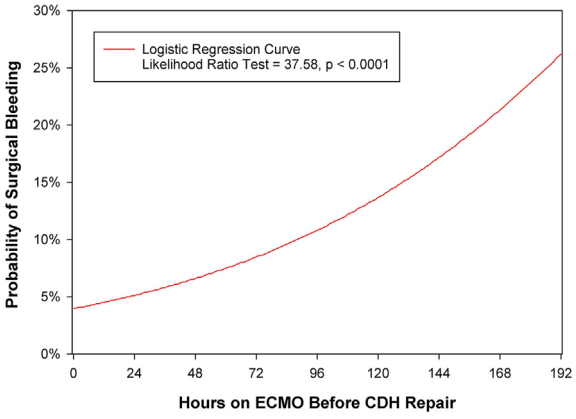

Fig. 1. The multivariable logistic regression and the likelihood ratio test demonstrated that the delayed CDH repair on ECMO increases the risk of surgical site bleeding.

(95% CI: 3.48–39.3, $p < 0.001$, Fig. 1). The risk of bleeding progressively increased with later surgical repair following ECMO cannulation, with a bleeding complication rate of up to 67% for operations occurring >10 days (Fig. 2). The BUN on the day of repair was markedly elevated among those infants who bled (median 63 mg/dL, IQR 20–85) compared to those who did not (median 9 mg/dL, IQR 7–13) ($p < 0.0001$), while Cr level showed no difference between groups. Among the 21 patients with surgical bleeding, 17 (81%) had BUN/Cr > 20 compared to only 33 of 125 (26%) non-bleeders ($p < 0.0001$, Table 3) The number of different operating surgeons totaled 23, with 19 surgeons performing 1–6 cases each equaling 43 cases, and 4 surgeons performing 16–39 cases each equaling 103 cases. Of the 21 cases complicated by surgical bleeding, 18 of them were performed by one of the 4 surgeons with highest CDH case volume. No difference in bleeding or other outcomes were found between different operating surgeons.

Multivariable logistic regression analysis demonstrated the timing of CDH repair and BUN elevation as significant predictors of surgical bleeding. There was a robust positive correlation between delayed timing of repair and BUN elevation such that these variables could not be soundly separated from one another in the analysis (Pearson $r = 0.83$, $p < 0.001$, $n = 146$). Among 44 DR patients, the area under the curve for BUN to predict surgical bleeding was 0.868 (95% CI: 0.761–0.976). A cutoff value of BUN >52 mg/dL gave sensitivity 81% and specificity 82%. Other variables tested by regression modeling that were not significantly predictive of surgical bleeding included CPR, gestational age, inborn status, and year of repair. Larger defect size actually predicted lower surgical bleeding risk, although the bleeding rate for the baseline comparison defect size A was unusually high (36%) making this finding of questionable utility. Additionally, acute renal failure requiring dialysis following CDH repair had a high correlation with bleeding (52% vs. 12%, $p = 0.0002$) (Table 3). Abdominal compartment syndrome related to surgical bleeding contributed to 42% of cases of renal failure requiring hemodialysis.

Examples found in our reviews of the medical records that could be used to define patients as being "unstable" included requirement of multiple vasopressors, fluid avidity, persistently elevated lactate levels, cardiac stun, poor ECMO flows with or without concern for improper ECMO cannula position, concern for neurologic injury, and concern for sepsis. When we applied this retrospective determination of instability found by review of progress notes, 35% of patients in the overall study cohort would be included, which would account for 31% of patients in the early repair group, and 42% of patients in the delayed repair group ($p = 0.23$).

The details of timing, bleeding source, and interventions for postoperative hemorrhage were tabulated for the 21 patients with bleeding (Table 5). Bleeding manifest by postoperative day 1 in 60%, but as late as day 6. Obvious hemothorax with chest tube

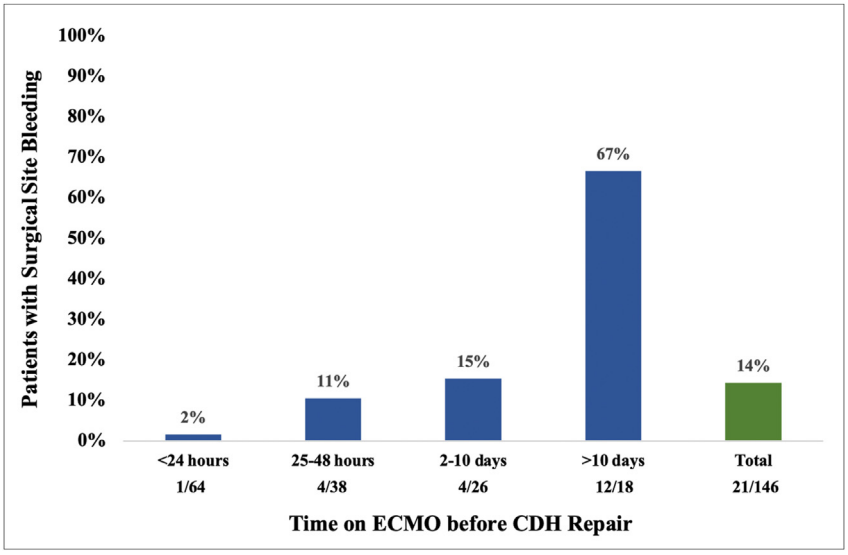

Fig. 2. The risk of surgical site bleeding increased with a longer time on ECMO before CDH repair, up to a rate of 67% for operations occurring >10 days.

Table 3
Effect of uremia on surgical bleeding.

Bleeding at surgical site	Overall (n = 146)	Surgical Bleeding (n = 21, 14%)	No Surgical Bleeding (n = 125, 86%)	p
BUN (mg/dl), median (IQR)	9 (7–16)	63 (20–85)	9 (7–13)	<**0.0001**
Cr (mg/dl), median (IQR)	0.6 (0.5–0.7)	0.7 (0.5–0.9)	0.6 (0.5–0.7)	0.25
BUN/Cr	15 (11–33)	73 (35–114)	14 (11–22)	<**0.0001**
BUN/CR > 20	50 (34%)	17 (81%)	33 (26%)	<**0.0001**
ARF (required dialysis), n (%)	26 (18%)	11 (52%)	15 (12%)	**0.0002**
Survival, n (%)	86 (59%)	12 (57%)	74 (59%)	0.81

BUN: blood urea nitrogen; Cr: creatinine; ARF: acute renal failure; IQR: interquartile range. Bold = P value statistically significant.

output as high as 250 cc per day, and tense abdominal distension, often accompanied by abdominal compartment syndrome physiology, or both made the diagnosis of severe operative bleeding apparent. Two patients were managed by placing additional larger caliber chest tubes and cessation of anticoagulation, while all others had repeat laparotomy or thoracotomy for decompression and hemostasis. Seven patients required multiple repeat operations to achieve surgical control of bleeding. For 11 patients, these repeat interventions failed to identify a clear source of bleeding. Bleeding sources such as the omentum, liver surface, or posterior diaphragmatic suture line were managed by standard surgical techniques including suture ligation, cautery, direct pressure, and hemostatic topical agents. Utilization of wound vacuum therapy with no fascial closure (i.e. an "open abdomen") was also a common strategy.

Patients had a longer duration of ECMO support in the DR group, a median of 18 days (IQR 11–25) compared with a median of 13 days (IQR 8–20) in the ER group ($p = 0.005$). Multivariable linear regression was performed to evaluate determinants of ECMO duration. Variables included CPR, stroke, cardiac defect, gestational age, renal failure, surgical bleeding, defect size, and timing of repair. Renal failure, surgical bleeding, defect size, and timing of repair were found to be significant. Renal failure requiring dialysis increased the mean duration of ECMO support by 6 days, bleeding by 10 days, defect size by 3 days per CDHSG category, and DR repair >48 h by 5 days.

Overall survival for infants with CDH repaired on ECMO was 59% and was not significantly impacted by the timing of repair. Multivariable logistic regression was performed to determine predictors of mortality. Defect size ($p = 0.05$), birth weight ($p = 0.043$), cardiac defects ($p = 0.013$), acute renal failure ($p = 0.004$), and duration of ECMO ($p < 0.0001$) were found to be significant covariates. Although it was seen to correlate with renal failure, surgical bleeding was not in itself associated with increased mortality.

Table 4
Outcomes within different time periods.

	Patient	Bleeding	Survival
1995–1999			
ER	17 (77%)	3 (18%)	9 (53%)
DR	5 (23%)	0	3 (60%)
Total	22 (100%)	3 (14%)	12 (55%)
2000–2004			
ER	21 (70%)	0	14 (67%)
DR	9 (30%)	2 (22%)	7 (78%)
Total	30 (100%)	2 (7%)	21 (70%)
2005–2009			
ER	25 (83%)	0	12 (48%)
DR	5 (17%)	2 (40%)	4 (80%)
Total	30 (100%)	2 (7%)	16 (53%)
2010–2014			
ER	17 (55%)	1 (6%)	10 (59%)
DR	14 (45%)	6 (43%)	5 (36%)
Total	31 (100%)	7 (23%)	15 (48%)
2015–2018			
ER	10 (50%)	1 (10%)	9 (90%)
DR	10 (50%)	5 (50%)	5 (50%)
Total	20 (100%)	6 (30%)	14 (60%)
2018–2021			
ER	12 (92%)	0	7 (58%)
DR	1 (8%)	1 (100%)	1 (100%)
Total	13 (100%)	1 (8%)	8 (62%)
1995–2021			
ER	**102 (70%)**	**5 (5%)**	**61 (60%)**
DR	**44 (30%)**	**16 (36%)**	**25 (57%)**
Total	**146 (100%)**	**21 (14%)**	**86 (59%)**

Bold = P value statistically significant.

Given the long time period covered by our data, we examined for any changes over time that may have occurred related to timing of repair, bleeding, and survival (Table 4). The rate of delayed OR timing ranged 17–30% during the first 15 years of the study, and increased to 45–50% from 2010 to 2018. Thereafter, 2018–2021, delayed repair became unusual. This resulted in higher bleeding complication rates during the time period 2010–2018. The survival was quite steady through out the entire study period, although with variability that can accompany overall small patient group size.

4. Discussion

During the initial time period of this study from 1995 to 2010, our center traditionally preferred early surgical repair on ECMO for infants with CDH. This preference had evolved during the late 1980s and early 1990s. The initial operative repairs on ECMO were historically fraught with severe bleeding complications, until we reported in 1993 and 1994 about the use of aminocaproic acid for operations performed while on ECMO [6,13]. Secondly, early repair was favored to avoid operations under conditions of progressive tissue edema and fluid overload that can be associated with the initial resuscitation phase of ECMO, likely related to the degree of cardiopulmonary compromise and the systemic inflammatory response to ECMO.

There is no consensus internationally on the definition of early repair. Several studies have used 24–72 h from ECMO initiation to represent early repair [2,4,10–12]. We considered early repair as timing within the first 48-h on ECMO based on the most common timing in the literature coupled with the above noted clinical findings related to progressive fluid overload. Our current protocol for CDH management on ECMO incorporates surgical repair within the first 24 h following ECMO initiation, largely based on the <2% surgical bleeding risk from the data review in this study.

In this retrospective review, we noted more variability in our timing of repair 2010–2018. The transition in timing strategy was not by protocol design per se, until our internal data review in 2018. Rather, it followed the accrual of literature suggesting that the timing of repair may not impact survival [18]. Our typical strategy had remained early repair; however, the emphasis on the early repair was no longer deemed critical and was up to the individual surgeon and ICU team's clinical judgement. Nonetheless, as depicted in Table 4, there was still a moderate proportion of delayed operations throughout the entire study period. For infants that did not have an early repair in the first 48 h, we have generally preferred repair later in the ECMO run rather than repair after decannulation. In our series, only 3 patients over 25 years had CDH repair following ECMO decannulation. Consequently, this study cannot address the outcomes of CDH repair on ECMO versus after ECMO.

Why were some repairs early and others delayed? Based on this retrospective review, we did not identify any specific physiologic factors that consistently contributed to the decision for timing of repair. We initially postulated that individual patient factors or “instability” may have played a role in decisions about operative timing. We valiantly tried to query physiologic data and progress note narratives regarding the timing of repair, but found this elusive in this retrospective review. Defining the concept of “instability” on ECMO, and whether it should affect timing of operative repair would seem to be important variables to understand. What was interesting, nearly as often as the medical record may have suggested that patient instability warranted delaying the CDH repair, for other cases, the same reasons were given for proceding with early CDH repair. Ultimately, we could not identify any data to indicate that the infants in the DR group were “sicker” than those in the ER group. The fact that the overall survival from both cohorts was equivalent (60% for ER and 57% for DR, $p = 0.737$) further suggested they were comparable.

It is interesting to note that while our study spans three decades, the foundational principles guiding CDH management did not substantively change over that time period. Gentle ventilation with conventional ventilator modes was favored throughout, with high frequency oscillation only used as a rescue method. ECMO management was likewise quite standardized during the entire time period, with only the heparin titration lab test regimens evolving as

Table 5
Details of patients with postoperative hemorrhage.

Bleeder	Year	Side	BUN	Day of repair after ECMO	Post-op day of bleeding	Location	Source	Treatment	Survival
1	1995	L	8	1.5	3–7	Chest tube, abdomen	Unclear	Ex-lap, washout, JP drain	No
2	1998	R	9	0.6	1	Chest tube, abdomen	Unclear	Ex-lap, washout	Yes
3	1999	R	14	1.7	4	Abdomen	Retroperitoneum	Ex-lap, washout	No
4	2000	L	29	8	1,5	Chest tube, lung, abdomen	Omentum	Ex-lap x 2, washout, suture	Yes
5	2000	R	53	13	5	Airway, chest	Lung, airway	Thoracotomy, washout, bronch	Yes
6	2007	L	31	8	5	Abdomen	Unclear	Ex-lap, washout, JP drain	Yes
7	2008	L	34	3.4	6	Abdomen, chest	Unclear	Ex-lap, washout, abdominal VAC	Yes
8	2012	L	93	14	1	Abdomen, chest	Posterior patch suture line	Ex-lap, suture ligation	No
9	2013	R	63	13	1	Abdomen	Liver surface	Ex-lap, VAC	Yes
10	2013	L	72	17	1,4	Abdomen	Unclear, then omentum	Ex-lap × 2, VAC	Yes
11	2014	R	8	1.2	5–17	Abdomen, bladder	Unclear	Ex-lap, JP drain	No
12	2014	L	58	9	1,2	Abdomen	Omentum	Ex-lap × 2, VAC	Yes
13	2014	R	105	18	1–7	Abdomen	Omentum, umbilical vein	Ex-lap × 4, VAC	No
14	2014	L	70	21	1–5	Chest	Unclear	New larger chest tube, output 250 cc/day × 3d	No
15	2015	R	11	1.9	1–3	Abdomen	Omentum, liver surface, abdominal wall	Ex-lap × 4, VAC	Yes
16	2015	R	90	14	1	Abdomen	Unclear	Ex-lap, VAC	Yes
17	2015	R	70	20	1–14	Abdomen and chest	Unclear	Ex-lap, VAC, later thoracotomy	No
18	2016	L	74	21	1	Chest	Unclear	Ex-lap, washout via patch opening	No
19	2017	L	93	9	5–8	Abdomen	Omentum	Ex-lap × 2, VAC	No
20	2017	L	80	22	3–5	Chest	Unclear	New larger chest tube, output 250 cc/day × 3d	Yes
21	2020	L	99	28	6–9	Chest, abdomen	Unlcear	Thoracotomy × 2, fibrin glue	Yes

stated earlier. Our group has not transitioned to the use of direct thrombin inhibitors for anticoagulation for CDH patients on ECMO, so we cannot comment on potential effects this would have for surgical bleeding or other ECMO complications. One group has published about use of bivalirudin for ECMO in CDH neonates with good results, although there is no comparison with heparin usage in that report [25]. Lastly, aminocaproic acid was used by standard protocol in all cases, and the same approach of open laparotomy with Gortex patch repair was utilized for all cases.

The overall rate of surgical bleeding in this study was 14% but was much lower with early repair following ECMO initiation at 5% (5/102). We additionally noted a progressive increase in bleeding with a longer duration of ECMO prior to repair (Figs. 1 and 2). Potential factors for higher risk of bleeding may include worsening coagulopathy with longer ECMO duration and a longer period of anticoagulation. Still, we did not have laboratory evidence by ACT, heparin levels, PTT or otherwise that could corroborate coagulopathy during later time points for any given patient's ECMO run. We did not utilize thromboelastogram evaluation for our anticoagulation protocols until very recently (2022), therefore, any potential impact remains speculative. Additionally, with increased fluid overload, the liver, spleen, retroperitoneum, and other tissues may become more fragile and likely to bleed during the perioperative period. These issues could be less prevalent with an early repair strategy. We do not have consistent data for daily fluid balance or volume status for all of the time periods in this study in order to move beyond speculation regarding this point.

It was interesting to find that surgical bleeding was not associated with higher mortality in our study. Nor did we have cases where urgent cessation of ECMO therapy was required to address bleeding. We maintained a steadfast philosophy that even if repeated laparotomies were necessary, along with periods of stopping anticoagulation, hemostasis could be eventually achieved. Likewise, if coming off ECMO earlier was going to clearly compromise survival potential related to ongoing poor lung function, even though it would obviously help achieve hemostasis for ongoing abdominal bleeding, we pushed forward with longer ECMO duration, as evidenced by a few patients being on ECMO upwards of 40 days. That being said, we did not have any survivors with ECMO duration beyond 38 days.

It was striking that a large percentage of patients with surgical bleeding had associated high (often very high) BUN levels on the day of operation. Severe uremia is known to cause platelet dysfunction which may impact bleeding risk [26]. Azotemia was likely related to aggressive diuresis and/or ECMO ultrafiltration in an effort to decrease tissue edema to facilitate surgical repair and improve lung function. We did not see significant BUN elevation in the ER group as this would take several days to manifest, whether in the setting of renal dysfunction or aggressive diuresis. Azotemia may therefore be a modifiable risk factor, and we recommend careful consideration before infants undergo CDH repair on ECMO with profound azotemia with BUN>50. Renal dysfunction needing hemodialysis was generally a postoperative phenomenon, especially in cases with preoperative BUN elevation (with preserved urine output) that developed postoperative abdominal compartment syndrome related to bleeding.

In this study, a shorter total duration of ECMO therapy was observed in the early repair cohort by a median of 5 days. This difference was statistically significant, but several other factors also impacted ECMO duration, including defect size, a reliable marker for disease severity. Surgical bleeding also had a significant impact on ECMO duration. Indeed, patients with surgical bleeding often required one or more additional operations to achieve hemostasis, abdominal decompression, and overall stability. Renal failure was another significant variable for increased ECMO duration exacerbated by abdominal compartment syndrome resulting from postoperative bleeding.

This study did not demonstrate a survival difference for early vs. delayed repair while on ECMO. Published reports on this topic have shown mixed results, with some advocating early repair based on improved survival [10–12,27,28] and other studies reporting improved survival with repair after ECMO decannulation [16–18]. Larger reports based on the CDHSG have also had mixed results, and it remains challenging to prove that the timing of CDH repair for infants that require ECMO is a significant factor regarding mortality [19]. Indeed, infants with CDH who require ECMO are a higher risk cohort than those successfully treated without ECMO. Hidden mortality related to deaths in unrepaired patients is an important consideration when looking at this dilemma. A more recent study utilizing propensity score matching from the CDHSG reported lower mortality with repair on ECMO compared to repair after ECMO and favoring early repair to delayed repair [4]. It is challenging to determine the optimal timing for repair as a factor contributing to survival, given the wide range of results from these retrospective studies. However, CDH repair itself is a requirement for ultimate survival, even though other patient and treatment factors influence survival in addition to the timing of repair.

Limitations of this study include its retrospective nature and single-center patient population. Our center has historically preferred early CDH repair for patients on ECMO. Therefore, patients who had delayed repair on ECMO may have clinical differences from early repair patients that are difficult to ascertain from a retrospective chart review. Broadening multicenter database collection with common variables and definitions to include timing of repair, surgical bleeding, and other morbidities associated with CDH repair on ECMO will aid in future studies.

5. Conclusions

We demonstrate a significantly increased risk of bleeding for delayed CDH repair on ECMO. Profound azotemia during ECMO was found to be an independent, potentially modifiable risk factor for surgical bleeding associated with delayed CDH repair on ECMO. Duration of ECMO was significantly longer with delayed repair, but there was no statistically significant difference in mortality with the timing of repair.

Declaration of Competing Interest and funding

The authors have no sources of financial support or conflicts of interest to declare.

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